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Androgen-Responsive Aspects of Cognition in Girls with Turner Syndrome

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Turner syndrome (TS) represents a unique, sex hormone-deficient model in which to study the biological effects of androgen treatment (replacement) on cognition in females because TS girls have gonadal dysgenesis and absent ovarian androgen and estrogen production. We investigated the effects of androgen replacement therapy in TS girls, ages 10–14 yr, on cognitive function. A total of 64 TS girls were randomized to receive oxandrolone or placebo for 2 yr. They had a cognitive evaluation of four domains (verbal abilities, spatial cognition, executive function, and working memory) at baseline, 1, and 2 yr of the study. In addition, all subjects were examined for study safety every 6 months.

Three of the four domains studied did not change significantly in response to oxandrolone treatment (verbal abilities, spatial cognition, and executive function). In contrast, the working memory summary score had a significant group by time interaction. The oxandrolone-treated group demonstrated improved performance after 2 yr, compared with the placebo group (P < 0.03). Minimal or no side effects were observed. In conclusion, oxandrolone treatment for 2 yr improves working memory in adolescent girls with TS. What this degree of improvement will mean in real life terms for TS girls remains to be determined. (*J Clin Endocrinol Metab* 88: 292–296, 2003)

TURNER SYNDROME (TS) arises in females who lack all or part of the second X chromosome and occurs in approximately 1 of every 2000 female births. The ovaries apparently form normally at conception and involute prematurely at 4–5 month gestation in girls with TS (1). As a result of this gonadal dysgenesis, the children lack ovarian estrogen and androgen production, do not undergo spontaneous pubertal maturation, and are infertile (2). Because the ovary normally produces 50% of circulating androgens in females, androgen levels are decreased in both adolescent and adult TS females (3, 4). TS therefore represents a unique, sex hormone-deficient model in which to study the biological effects of androgen treatment (replacement) on cognition in females.

The features of the TS phenotype include short stature and congenital malformations such as webbing of the neck and coarctation of the aorta (5). In addition, these females manifest a specific neurocognitive profile in which verbal ability [including verbal intelligence quotient (IQ)] is generally normal (6–9), whereas spatial cognition (visual-spatial/perceptual, visual-motor), working memory, and executive function (planning, organizing) are relatively impaired (10–15). Previous neuroanatomic studies demonstrated differences in the right posterior regions (parietal and temporal), the bilateral dorsolateral prefrontal cortex, the caudate nucleus, and the left parietal-perisylvian region in TS subjects, compared with controls (16–19), that may be related to their cognitive differences.

These TS-associated cognitive deficits could be due to the absent ovarian production of estrogen and androgen as well as haploinsufficiency for gene/genes on the X chromosome. Certain of the TS deficits, such as speeded motor performance, may be secondary to estrogen deficiency because estrogen replacement is associated with improvement (20, 21). Other TS cognitive deficits, including spatial function, are apparently not ameliorated by estrogen replacement and may occur secondary to androgen deficiency. Androgen alterations during the perinatal period and puberty influence cognitive function and behavior in animal and human models, and sex differences have been observed in several cognitive areas, including visual-spatial tasks involving mental rotation and spatial perception (22).

These observations led us to hypothesize that androgen replacement therapy in TS females would improve performance in specific cognitive domains known to be impaired, including spatial cognition, working memory, and executive function. TS girls, ages 10–14 yr, were enrolled in a randomized, placebo-controlled longitudinal study and were treated with the androgen oxandrolone or placebo for 2 yr. Oxandrolone has been used to stimulate growth in TS girls for more than 20 yr (23, 24) without any adverse side effects. This study, in contrast, examined the effects of oxandrolone on cognition in TS.

Subjects and Methods

This study was approved by the Human Studies Committee at Thomas Jefferson University and the National Institute of Child Health

Abbreviations: IQ, Intelligence quotient; SES, socioeconomic status; SGPT, serum glutamate pyruvate transaminase; TS, Turner syndrome; WISC-R, Wechsler Intelligence Scale for Children-Revised.

and Human Development. Informed consent and assent were obtained in all cases.

The study used a double-blind, placebo-controlled design. Patients were randomized at baseline (derived from tables of random numbers in blocks of eight) to receive treatment with either oxandrolone (0.06 mg/kg·d po; Bio-Technology General Corp., Iselin, NJ) or placebo. The randomization was performed by the NIH Clinical Center Research Pharmacy. All TS children also received GH (Humatrope, Eli Lilly & Co., Indianapolis, IN) injections (0.05 mg/kg·d sc). A detailed cognitive and physical evaluation was performed at baseline and again at 1- and 2-yr intervals. No patient received estrogen during the 2-yr study interval. Study drug compliance was assessed by the patient diaries and by counting the pills that patients brought back.

All study participants were monitored for any side effects related to androgen therapy every 6 months. The evaluation included measurement of blood pressure, a physical examination to assess significant clitoral enlargement (>1 cm), acne, or hirsutism, and liver function tests. According to the protocol, if any of these side effects were observed, the dosage of oxandrolone or placebo was reduced by 50%, and the patient was reevaluated at the next study visit.

Subjects

Sixty-four TS subjects (ages 10.0–14.9 yr) began the study, 51 subjects completed the 2-yr cognitive study requirements, and their data are presented. Attrition was limited to five patients: three withdrew because they were satisfied with height and development at the end of 1 yr, and two patients were lost to follow-up soon after the initial study visit. Their data are not included in the cognitive analysis. Cognitive outcome was the primary endpoint of the study, and growth outcome was a secondary endpoint. The data for height outcome are not yet available for analysis.

Six cases were excluded from the neuropsychological data analyses described below because they did not meet the inclusion study criteria for verbal IQ above 69. These exclusionary criteria were implemented because such children demonstrate more diffuse developmental delay than is typical in TS. We applied the Dixon Gap Rule (25) to the TS population upper distribution for verbal IQ and performance IQ. Accordingly, two individuals with performance IQ greater than 130 were eliminated from the analyses because they were statistical outliers.

The diagnosis of TS was confirmed by karyotyping. A total of 43% were 45,X, and the remainder were mosaic or had a nonmosaic partial deletion of one X chromosome. No subjects had a Y component to their karyotype. None had previously been treated with androgen, estrogen, or GH.

Statistics

We performed a repeated measures ANOVA addressing the change in summary score at 1 and 2 yr, compared with the baseline. Dichotomous variables such as race were compared by χ^2 analysis. All statistical tests were two-tailed tests, and the results are presented as mean ± SD for tabular results. P values less than 0.05 were considered statistically significant. Using a statistical power analysis, we calculated that with $n = 52$ subjects, there would be an 80% power to detect a moderate effect size of 0.8 at $\alpha = 0.05$, two-tailed t test of means.

Summary scores represent the sum of one to three component tests, each converted to Z-scores. Z-scores were derived from a normative sample of 26 prepubertal control females whose age and socioeconomic status (SES) were similar to the entire TS group at baseline and who were tested contemporaneously in the same laboratory.

Design and procedures

SES levels were derived from the Hollingshead 2-Factor Index of Social Status (26), on the basis of education and occupation of parents.

Materials

Neuropsychological measures were administered in a standardized manner by trained psychometricians who were blinded to treatment assignment. All testing was conducted at Thomas Jefferson University Hospital and the National Institutes of Health. A certified school psychologist reviewed all results.

Intelligence was assessed with the full administration of the Wechsler Intelligence Scale for Children-Revised (WISC-R; Ref. 27). Subtest scaled scores were used for deriving the Kaufman factor scores (28). The WISC-R is a widely used, individually administered measure of intellectual functioning for children ages 6.0–16.9 yr. The most recent version (WISC-III) was not used because the study was started before its widespread use (1991–1992).

Summary scores (Table 1) were computed for verbal abilities, spatial cognition, working manipulative memory, and executive function on the basis of neuropsychological test performance.

Results

The two TS groups (oxandrolone and placebo) were well matched for baseline demographics, including age, SES, race, handedness, and the proportion of nonmosaic 45,X subjects (Table 2).

Cognitive results

Results from four summary scores (verbal abilities, spatial cognition, working memory, and executive function) are presented in Table 3. Both TS groups had similar performance at baseline for all summary scores. Verbal abilities were normal at baseline and did not change over the study interval. Both TS groups had deficits in spatial cognition at the baseline that did not change over the 2-yr observation interval. Executive function was also normal at baseline and improved slightly in both groups by the second year.

In contrast, the two TS groups differed significantly in change in working memory summary score over the 2-yr treatment interval. The oxandrolone-treated group demonstrated improved performance after 2 yr, compared with the

TABLE 1. Neurocognitive evaluation

Cognitive domain	Test
General cognitive skills	WISC-R (27)
Working memory	
Visual	WISC-R Digit Span-Backward scales (27)
Verbal	Missouri Auditory Verbal Learning Test, immediate recall (45)
Spatial cognition	WISC-R Perceptual Organization Factor (picture completion, picture arrangement, block design, and object assembly scales (28)
	Rey-Osterrieth Complex Figure-Copy (46)
	Beery Test of Visual Motor Integration standard score (47)
Executive function	Wisconsin Card Sort Test, % errors (48)
	Tower of Hanoi (49)
Verbal abilities	Verbal Comprehension Factor (information, similarities, vocabulary, and comprehension scales) (28)

TABLE 2. Demographic information

	TS			Controls
	Oxandrolone	Placebo	P	
n	26	25		26
Chronological age (yr)	11.8 ± 1.5	12.0 ± 1.6	0.57	11.6 ± 0.8
SES	47 ± 12	49 ± 13	0.47	51 ± 11
Caucasian (%)	77	72	0.81	96
Right handed (%)	88	80	0.51	88
45,X (%)	50	36	0.14	

TABLE 3. Summary score results (TS)

	TS-oxandrolone			TS-placebo			P^a
	Baseline	Yr 1	Yr 2	Baseline	Yr 1	Yr 2	
n	26	26	26	25	25	25	
Working memory	−1.2 ± 1.3	−0.7 ± 1.7	−0.3 ± 1.4	−0.8 ± 1.7	−0.5 ± 1.2	−1.0 ± 1.5	0.03
Δ[b]		0.5 ± 1.3	0.9 ± 1.5		0.3 ± 1.3	−0.1 ± 1.2	
Spatial cognition	−2.8 ± 2.4	−2.7 ± 2.7	−2.6 ± 2.9	−3.1 ± 3.6	−2.8 ± 2.8	−2.8 ± 3.1	0.89
Δ		0.1 ± 1.9	0.2 ± 1.8		0.2 ± 1.7	0.2 ± 1.7	
Executive function	0.5 ± 1.3	0.6 ± 1.4	0.9 ± 1.5	0.5 ± 1.2	0.5 ± 1.2	1.0 ± 1.3	0.86
Δ		0.1 ± 1.4	0.4 ± 1.4		−0.1 ± 1.5	0.4 ± 1.2	
Verbal abilities	−0.1 ± 1.6	0.0 ± 1.6	−0.3 ± 1.9	0.0 ± 1.8	−0.3 ± 1.7	−0.3 ± 1.7	0.37
Δ		0.1 ± 0.9	−0.2 ± 1.3		−0.3 ± 1.0	−0.4 ± 0.8	

Data are expressed as mean ± SD.
[a] ANOVA of comparison of oxandrolone and placebo groups.
[b] Change from baseline at 1 and 2 yr.

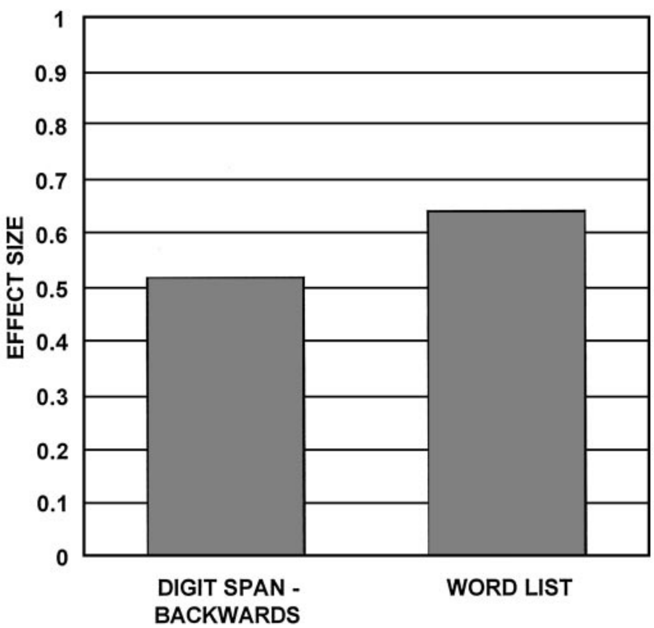

FIG. 1. The treatment effect size (oxandrolone group mean minus placebo group mean divided by the placebo group SD) of the two component tests of the short-term manipulative memory summary score, derived for the 2-yr Δ from baseline.

TABLE 4. Adverse events associated with oxandrolone (after baseline visit)

	Oxandrolone	Placebo
SGPT increase[a]	2	1
Virilization[b]	3	0
Hypertension[c]	1	1

[a] SGPT >100 U/liter, upper limit of normal = 41.
[b] Defined as unusual acne, hirsutism, clitoral changes.
[c] Diastolic blood pressure >89 mm Hg; rise occurring after baseline visit.

placebo group (Table 3). The placebo group demonstrated a deterioration in performance, whereas the oxandrolone group had a gain in performance. The oxandrolone treatment effect size for the two components of the working memory summary score was 0.52 ± 1.0 and 0.64 ± 1.0, for digit span-backward and word list-immediate recall, respectively, which is approximately half a SD difference between the treated and untreated TS groups (Fig. 1).

Drug safety

We compared the incidence of potential androgen-associated side effects, including alteration in liver function or hypertension (Table 4). The increased serum glutamate pyruvate transaminase (SGPT) was mild, occurred in a total of three subjects, and decreased to normal on subsequent visits (data not shown). The incidence of hypertension was similar in both groups. We also examined patients for potential virilizing changes associated with androgen, including clitoromegaly, excessive acne, and hirsutism. No patient experienced unusual hirsutism or acne. Mild clitoromegaly occurred in three oxandrolone-treated patients and regressed after a 50% dose reduction.

Discussion

The results are consistent with our hypotheses that androgen replacement in TS girls has a positive effect on specific areas of cognitive ability. Significant improvement was seen in the working memory summary scores after 2 yr of treatment with oxandrolone but not placebo. In contrast, no significant differences were observed between the oxandrolone-treated and placebo-treated TS groups in the verbal abilities, spatial cognition, or executive function summary scores. The improvement in working memory performance appeared to reflect a cumulative effect over the 2-yr course of the study. Additionally, it is important to note that, although the working memory summary score improved significantly in the oxandrolone-treated TS group, performance, on average, remained minimally impaired.

The pattern of androgen-related change in these tasks has not been previously reported, to our knowledge. Although initially seeming dissimilar, these tasks have a similar conceptual underpinning. All require the subject to briefly store and rapidly manipulate bits of information. This information was in one task verbal (verbal learning, immediate recall) and in another task numerical (digit span-backward; Ref. 29). The abilities required for these tasks such as storing, manipulating, and retrieving information are commonly attributed to working memory (30). It would seem appropriate to conclude that the impact of androgen treatment on cognitive function in TS is, therefore, on working memory.

Working memory relies on a distributed neural network with frontal circuitry and has previously been described as impaired in TS children and adults (15, 31). In addition, TS-associated frontolimbic differences in neuroimaging studies have been reported in TS adults (16) and children (17, 18). The nature of the oxandrolone effect on these systems is unclear, but it is consistent with previous reports suggesting that sex steroids act on short-term manipulative or working memory (32). Recently, Haberecht *et al.* (19) demonstrated by functional magnetic resonance imaging in TS females that frontal-parietal and frontal-striatal neural network alterations may lead to working memory impairment. TS adolescents in that study tended to overuse posterior structures and underuse/activate frontal structures when working memory demands increased. It is possible that androgen treatment in TS increases frontal efficiency, allowing individuals to keep information fresh in mind in the face of distracting or competing information. Alternatively, androgen may lead to reorganization of neuronal systems within these regions that improve the efficiency of working memory. The time requirements for the improvement (2 yr) would support a reorganization effect.

This improved working memory performance did not appear to be secondary to augmentation of general verbal ability. Performance on the verbal abilities summary score, which includes tests of auditory language comprehension and receptive vocabulary, changed minimally in both groups.

There were no significant differences in performance of the oxandrolone-treated *vs.* placebo-treated TS groups on the spatial cognition summary score after 2 yr of treatment. This summary score reflects performance on tasks assessing both visual-spatial perception and visual-constructional abilities. Because TS females differ from controls to the greatest extent in these abilities and this cognitive domain appears to be most susceptible to androgen deficiency and treatment, we would have expected to find androgen treatment effects. Our lack of findings may be related to the age of the subjects, the dose of medication, the treatment duration, the particular androgen used, or other unknown factors.

In addition, no apparent androgen-related effects on executive function were observed in the TS subjects. Working memory and executive function have been functionally linked. Therefore, a positive benefit on the former would potentially be linked to a positive benefit on the latter. This was not the case, perhaps due to the tasks chosen or the reasons listed above.

The current findings suggest that estrogen and androgen effects on cognition in TS females can be disassociated, consistent with previous models of sex hormone effects on cognition. Most of these models emphasize the effect of androgen on spatial ability and the effects of estrogen on motor function and verbal memory. We previously demonstrated positive effects of estrogen on nonverbal processing speed and speeded motor function in TS adolescent (20, 21). In contrast, androgen treatment affects a different cognitive domain in this study, *i.e.* working memory. A potential confounder for dissociating the androgen *vs.* estrogen central nervous system effects is the aromatization pathway converting androgen to estrogen. Because oxandrolone is a nonaromatizable androgen and cannot be converted to estrogen, our results were specifically androgen-mediated. Although any treatment effects observed in the oxandrolone-treated TS group were most likely secondary to the oxandrolone alone, we cannot exclude the possibility that the combined treatment with both androgen and GH could result in a particular/steroid/GH interaction that would differ from androgen alone.

Both animal and human studies have shown clear-cut structural effects of both androgen and estrogen on subcortical nuclear regions such as the hypothalamic/preoptic area as well as forebrain regions that are related to behavior (33–35). Androgen alterations during the perinatal period and puberty influence cognitive function and behavior in animal models. Most of these animal studies in rats and monkeys have demonstrated either prenatal or early postnatal androgen-induced changes in spatial abilities or spatial memory associated with specific brain alterations (36–39).

Several lines of evidence support an association between androgen and spatial ability and, to a lesser extent, working memory in humans. The first relates to observed gender differences, the second to androgen deficiency and replacement states, and the last to unusual human models from nature. Males generally outperform females in visual-spatial tasks involving mental rotation, spatial perception, spatial visualization, and problem solving, which all rely to some extent on working memory (22). In addition, higher testosterone levels are correlated with superior spatial abilities (40) in normal women (ages 18–31 yr) and superior performance on the Mini-Mental State Examination (MMSE) and the "World" component of the MMSE (41) in elderly women (ages 55–99 yr).

Neuropsychological impairment occurs in subjects with androgen deficiency. Men with untreated, congenital, hypogonadotropic hypogonadism have diminished production of testosterone as well as impaired spatial ability, verbal memory, and attention relative to normal controls (42). Testosterone treatment of older men (60–75 yr) results in improved performance in the Wechsler Adult Intelligence Scale-Revised block design scale and improved working memory (32, 43).

Models from nature also support a positive effect of androgens on short-term manipulative or working memory abilities. Genetic males with testicular feminization syndrome, who lack androgen receptors and cannot respond to testosterone, had relatively impaired performance on the Wechsler Adult Intelligence Scale digit span subtest, compared with control males (44) and similar to our findings.

Overall, oxandrolone treatment appears to result in small but significant augmentation of working memory in TS children without affecting spatial cognition, verbal abilities, or executive function. Although the clinical instruments may not be perfect measures of specific abilities, the working memory summary score performance improved significantly over 2 yr in the oxandrolone-treated TS group. These positive results were observed despite study limitations, including the inherent difficulties of longitudinal testing of children and the small sample size. The doses of androgen used in this study were safe, without notable virilization side effects in girls. However, treating young girls with androgen (nonvirilizing) should still be regarded with some caution. Additionally, recommending androgen treatment of working memory deficits is premature. To be considered as a therapeutic modality, the benefits of treatment must always be balanced by consideration of potential risks.

Unanswered questions include what the optimal dose and dose duration for treatment would be and what the optimal time of initiation of treatment would be from the point of view of neural plasticity and development. The observation that incremental improvement was noted after 2 yr of treatment suggests that a longer treatment interval may be associated with additional improvement in these specific abilities. What is also unclear is the clinical significance of this degree of improvement or what this degree of improvement will mean in real life terms for TS girls. Future studies need to be done to assess the additional longitudinal effects and well as other outcome measures.

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